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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/989,758 | 11/20/2001 | Todd R. Golub | WIBL-POL-579 | 9648 |

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EXAMINER

FREDMAN, JEFFREY NORMAN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1637

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/989,758

Applicant(s)

GOLUB ET AL.

Examiner

Jeffrey Fredman

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 8, 15-20, 39 and 40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8, 15-20, 39 and 40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 104402, 1017105
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 4, 2006 has been entered.

Status

2. Claims 1-5, 8, 15-20 and 37-40 are pending.

Claims 1-5, 8, 15-20 and 37-40 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112 – first paragraph

3. Claims 1-5, 8, 15-20 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The sequences of Genbank Accession Numbers L20971 and M18255, which are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The sequence of these accession numbers is essential because, as evidenced by claim 1, the Genbank Accession numbers are specifically recited in the claims. Thus, in order to perform the method of the invention, it is essential to use the sequence

Art Unit: 1637

described by these accession numbers. Therefore, in order to properly enable this application, the sequences of the Genbank Accession Numbers must be added to the specification, and compliance with the other requirements of the Sequence Rules completed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-5, 8, 15-20, 39 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Alizadeh et al (Nature (February 2000) 403:503-511) as evidenced by Shipp et al (Nature Medicine (2002) 8(1):68-74).

Alizadeh et al teach a method of classifying a sample according to lymphoma type (see page 504, column 2, where “the algorithm segregated, with few exceptions, the recognized classes of lymphoid malignancies”) comprising:

(a) determining a gene expression profile of gene expression products from two or more informative genes, wherein the gene expression product is isolated from one or

Art Unit: 1637

more cells in the sample (see figure 1, where Alizadeh shows screening of the microarray with mRNA sample),

wherein the gene expression profile is correlated with a lymphoma type, thereby classifying the sample with respect to lymphoma type (see figure 1 and page 505, where Alizadeh demonstrates lymphoma type association with different gene expression profiles).

With regard to the association of L20971 (which is the PDE4B gene) and M18255 (which is the PKC beta gene) with treatment outcome, Shipp notes "We next investigated whether we could find support for our outcome predictor in the expression data of Alizadeh et al. Of the 13 genes in our supervised DLBCL outcome predictor, 3 were represented on the lymphochip: NOR1 (also known as NR4A3), PDE4B and PKC- (also known as PRKCB1). When evaluated as single markers in the dataset of Alizadeh et al., NOR1 ($P = 0.05$) and PDE4B ($P = 0.07$) were clearly correlated with outcome. Multiple PKC- cDNAs are present on the lymphochip; these clones gave discordant expression results in the DLBCL patients, perhaps reflecting varying degrees of specificity for the isoforms of PKC. However, two clones (clone 1308435 and 685194), specific for the PKC-2 isoform, were indeed correlated with outcome in the DLBCL patient series of Alizadeh et al. ($P = 0.04$). These results from an independent dataset confirm our initial observations and highlight the value of publicly accessible gene-expression databases for rapid, computational validation of hypotheses (see page 72, column 1)."

Shipp is citing the Alizadeh nature paper and states that the data provided for PDE4B and PKC beta, the two claimed genes, were correlated with treatment outcome. This provides direct evidence that Alizadeh inherently anticipates the current claims, since Alizadeh is expressly noted to have statistically significant results demonstrating the correlation of outcome with the expression of the two recited genes. As MPEP 2112 notes "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency)."

With respect to claims 2, 16-17, Alizadeh expressly teaches both diffuse large-cell lymphoma and follicular lymphoma (see page 504, column 1).

With respect to claims 3 and 18, Alizadeh teaches the use of mRNA pools to form the cDNA probes (see figure 1).

With respect to claims 3 and 19, Alizadeh teaches analysis of thousands of different cDNAs for the analysis (see figure 1).

With regard to claims 5 and 20, the cDNA microarray of Alizadeh (see figure 1) is comprised of cDNA which is an oligomer of nucleotides, thereby comprising an oligonucleotide.

With regard to claims 37-40, Alizadeh teaches the use of more than 10 informative genes (see figures 1-4).

Finally, with regard to claims 1 and 8, Alizadeh expressly teaches a correlation of gene expression profile with treatment outcome, including survival as shown in figure 5 and page 509, columns 1 and 2.

With regard to the elected genes, the supplementary information shows that Alizadeh utilized Bfl-1, Genbank Accession No. U29680 (attached).

Alizadeh also utilized an EST which is 98% identical to PDE4B (Genbank Accession No. L20971)(see alignment below)

```
>AA056218 AA056218 zf22e11.r1 Soares_fetal_heart_NbHH19W Homo sapiens cDNA  
clone IMAGE:377708 5', mRNA sequence. 2/97  
Length = 290
```

Plus Strand HSPs:

Score = 1350 (208.6 bits), Expect = 2.6e-55, P = 2.6e-55
Identities = 272/276 (98%), Positives = 272/276 (98%), Strand = Plus / Plus

```
Query:   3399 TTTGTAAGTTATTAATTTATATATCTAACATTGCCCTGCCAATGGTGGTGTAAATTTGTG 3458  
          || ||||||||||||||||||||||||||||||||||||||||||||||||||||  
Sbjct:   15  TTGGTAAGTTATTAATTTATATATCTAACATTGCCCTGCCAATGGTGGTGTAAATTTGTG 74  
  
Query:   3459 TAGAAAACCTCTGCCTAAGAGTTACGACTTTTTCTTGTAATGTTTTGTATTGTGTATTATA 3518  
          ||||||||||||||||||||||||||||||||||||||||||||||||||||  
Sbjct:   75  TAGAAAACCTCTGCCTAAGAGTTACGACTTTTTCTTGTAATGTTTTGTATTGTGTATTATA 134  
  
Query:   3519 TAACCCAAACGTCACCTTAGTAGAGACATATGGCCCCCTTGGCAGAGAGGACAGGGGTGGG 3578  
          ||||||||||||||||||||||||||||||||||||||||||||||||||||  
Sbjct:   135 TAACCCAAACGTCACCTTAGTAGAGACATATGGCCCCCTTGGCAGAGAGGACAGGGGTGGG 194  
  
Query:   3579 CTTTTGTTCAAAGGGTCTGCCCTTTCCCTGCCTGAGTTGCTACTTCTGCACAACCCCTTT 3638  
          ||||||||||||||||||||||||||||||||||||||||||||||||||||  
Sbjct:   195 CTTTTGTTCAAAGGGTCTGCCCTTTCCCTGCCTGAGTTGCTACTTCTGCACAACCCCTTT 254  
  
Query:   3639 ATGAACCAGTTTTTGGAACAATATTCTCACATTAGA 3674  
          |||||||||||||| |||||||||||||| ||||  
Sbjct:   255 ATGAACCAGTTTTNGAAACAATATTCTCACANTAGA 290
```

Alizadeh also utilized an EST which is 98% identical to PRKACB (Genbank

Accession No. M18255)(see Alignment below).

>AA837054 AA837054 od18b09.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone
IMAGE:1368281 similar to gb:X06318 PROTEIN KINASE C, BETA-I TYPE
(HUMAN);, mRNA sequence. 3/98
Length = 825

Minus Strand HSPs:

Score = 3119 (474.0 bits), Expect = 4.7e-137, P = 4.7e-137
Identities = 645/658 (98%), Positives = 645/658 (98%), Strand = Minus / Plus

```
Query: 657 GCATATATTAATTCAGTTTAATCATATCAATTCTTAAACAAAAAATTCCTCCAAGAGAC 598
      |||
Sbjct: 13 GCATATATTAATTCAGTTTAATCATATCAATTCTTAAACAAAAAATTCCTCCAAGAGAC 72

Query: 597 AATAGTTCACAGTAACTGCAAAGCTTACTCACAATTTTAAAAATATCGCTCATGCTTAG 538
      |||
Sbjct: 73 AATAGTTCACAGTAACTGCAAAGCTTACTCACAATTTTAAAAATATCGCTCATGCTTAG 132

Query: 537 CATTCAAAGAAGATATTATAGAATAACTGTAAAAACTTTTACCAGGAACATCAGCTTCTG 478
      |||
Sbjct: 133 CATTCAAAGAAGATATTATAGAATAACTGTAAAAACTTTTACCAGGAACATCAGCTTCTG 192

Query: 477 ACTTGAAAAATTACAAATACTGAAGCATTTTGGTATCAGACACAGTAGTTTGTGACATTGT 418
      |||
Sbjct: 193 ACTTGAAAAATTACAAATACTGAAGCATTTTGGTATCAGACACAGTAGTTTGTGACATTGT 252

Query: 417 CTGTTCAATTTGATGAGTTTCTGGAAGTTTGGAAAATTGTACCTCTATAATTGGATAATGC 358
      |||
Sbjct: 253 CTGTTCAATTTGATGAGTTTCTGGAAGTTTGGAAAATTGTACCTCTATAATTGGATAATGC 312

Query: 357 GCTTATTCTAAACTAAACATTTTCAAATGTAGAAAACAACTAGCAAGCTACACATACAA 298
      |||
Sbjct: 313 GCTTATTCTAAACTAAACATTTTCAAATGTAGAAAACAACTAGCAAGCTACACATACAA 372

Query: 297 AGAAAAGCCCTCTAAGACAAGCTTTCCACATGTTGAATGCCAGCATGTGCACCGTGAATC 238
      |||
Sbjct: 373 AGAAAAGCCCTCTAAGACAAGCTTTCCACATGTTGAATGCCAGCATGTGCACCGTGAATC 432

Query: 237 CTGGAAGACTAGAATTGATACATACGCTTGGCTTGAAGTCTTACACCCCAG-CTCAACGA 179
      |||
Sbjct: 433 CTGGAAGACTAGAATTGATACATACGCTTGGCTTGAAGTCTTACACCCCAGGCTCAACGA 492

Query: 178 TG-AGTTTGCATTACCTACACATTAATGACATACTCTGGGTAGTATAAGAGAAGCCAG 120
      ||
Sbjct: 493 TGGAGTTTGCATTACCTACACATTAATGACAAAACCTCTGGGTAGTATAAGAGAAGCCAG 552

Query: 119 CAAATTCATTTTGG-TCCAAGTTCATGATGAAGAGTTTATCAGTGGGGG-TCAGTTCAC 62
      |||
Sbjct: 553 CAAATTCATTTTGGGTCCA-GTTCATGATGAAGAGTTTATCAGTGGGGGGTC-GTTCAC 610
```



```

Query:      61  AGGCTG-TCTGGTGAACCTCTTTGTCTGAAGTTGGAGG-TGTCTCTCTTGTCTCTCTGCC 6
             |||||
Sbjct:     611  AGGCTGGTCTGGTGAACCTCTTTGTCTGAAGTTGGAGGGTGTCTCTCTGGGCTC-CAGCC 667

```

Finally, Alizadeh also utilized an EST which is 96% identical to HMGIY (Genbank Accession No. L17131)(see Alignment below).

```
>W73350 W73350 zd53h07.s1 Soares_fetal_heart_NbHH19W Homo sapiens cDNA clone
IMAGE:344413 3' similar to gb:M23614 Human HMG-I protein isoform mRNA
(HUMAN);, mRNA sequence. 10/96
Length = 412
```

Minus Strand HSPs:

Score = 1943 (297.6 bits), Expect = 1.2e-81, P = 1.2e-81
Identities = 399/412 (96%), Positives = 399/412 (96%), Strand = Minus / Plus

Query: 9978 CCAGAAAAGGATANNNNNNNNATTCAAGTAACTGCAAATAGGAAACCAGAGAGGGAGCCC 9919
 ||||||| |||||||
 Sbjct: 1 CCAGAAAAGGATATTTTTTTTATTCAAGTAACTGCAAATAGGAAACCAGAGAGGGAGCCC 60

```
Query:  9918 CAGGCTGGGACAAATCATGGCTACCCCTCCCCAACAGAAACAGGGGGAGGAGGTGGCCCCCT 9859
          |||||
Sbjct:   61 CAGGCTGGGACAAATCATGGCTACCCCTCCCCAACAGAAACAGGGGGAGGAGGTGGCCCCCT 120
```

```
Query:  9858 ACACCCCTTTATGGTCGATTCGGGGCCCCCTTGCTCACTCTGCTGCAGCATCCTAGGGGCGAG 9799
        |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct:  121 ACACCCCTTTATGGTCGATTCGGGGCCCCCTTGCTCACTCTGCTGCAGCATCCTAGGGGCGAG 180
```

Query: 9798 GGCCCCACCTTCCCTGGGACTGGGGTAGTCGGTCACCCAGCCTGCCATGCCCCAGCCCCT 9739
||||| |||||
Sbjct: 181 GGCCANAC-TTCCCTGGGACTGGGGTAGTCGGTCACCCAGCCTGCCATGCCCCAGCCCCT 239

Query: 9738 CTTCCCCACAAAGAGTATCTTGGGGGAGGGGATCGTGGGCAGAACAGGAGGCAATGAGGA 9679
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Sbjct: 240 CTTCCCCACAAAGAGTATCTTGGGGGAGGGGATCGTGGGCAGAACAGGAGGCAATGAGGA 299

Query: 9678 TGAACATTTGG- CGCTGGTAGCAGCAGCAATGACGGATGTCTGAAGAATGG- AACATTGAA 9621
 |||
 Sbjct: 300 TGAACATTTGGGCGCTGGTAGCAGCAGCAATGACGGATGTCTGAAGAATGGGAACATTGAA 359

```

Query:   9620 CAAAAAACAACACAACACTGTCCAGAGGTAGTTTGTGAACAGAGGAAAAATGGA 9569
          |||
Sbjct:   360 CAAAAAACAACACAACACTGTCCAGAGGTAGTTTGTGAACAGAGGAAAAATGGA 411

```

Response to Arguments

6. Applicant's arguments filed February 2, 2006 have been fully considered but they are not persuasive.

Applicant argues that the two sequences are definite. While this argument is persuasive, the sequence information in claims is critical subject matter that cannot be incorporated by reference. Therefore, the new 112, enablement rejection is made and Applicant must comply with the Sequence rules, providing the sequence for the two accession numbers and identifying the sequences by SEQ ID NO in order to overcome this rejection.


Applicant argues that the Alizadeh reference does not teach that the expression of the PDE4B and PKC beta genes were associated with treatment outcome. The newly cited Shipp reference evidences the fact that the Alizadeh reference does, in fact, provide a gene expression profile for these two genes which is "clearly correlated with outcome". Therefore, this rejection, as amended, is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jeffrey Fredman
Primary Examiner
Art Unit 1637

5/17/06